BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

Fig. 1

(prior art)

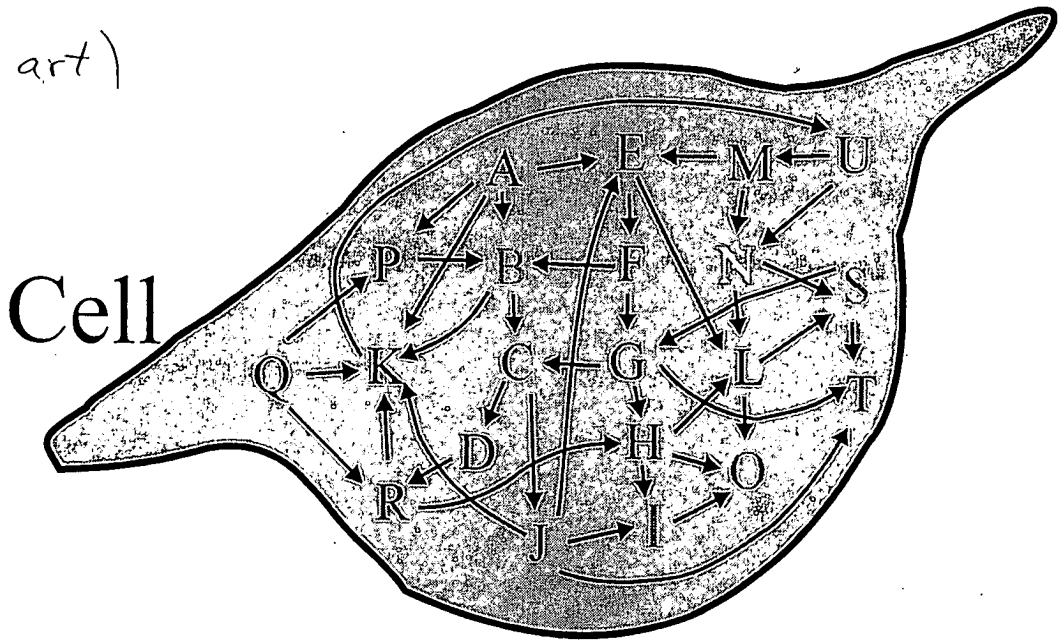


Fig. 2

(prior art)

MAP Kinase/Phosphoinositide/ PI3 Kinase Pathways in the Network

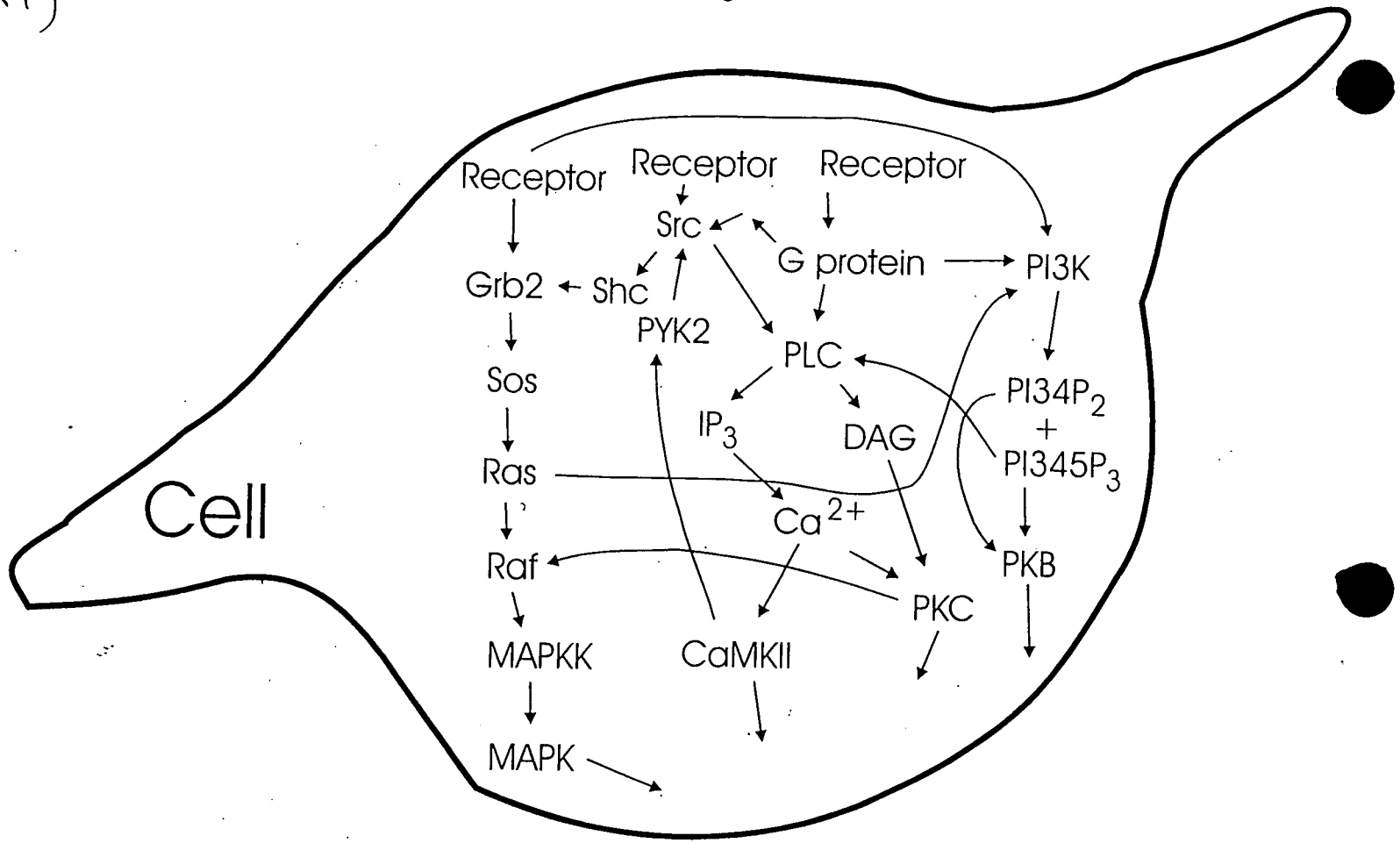
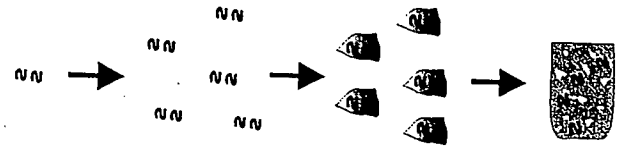


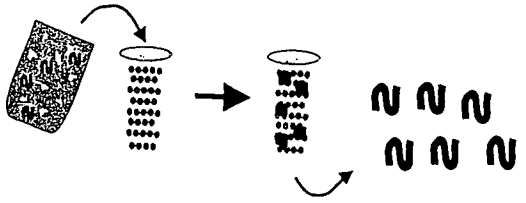
Fig. 3
(prior art)

Measurement of Kinase Activation (Current Technology)

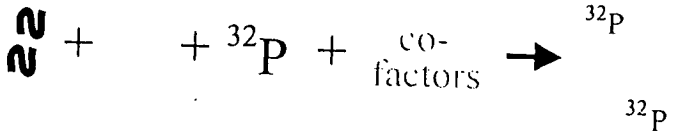
1. Grow up cells & prepare for assay (variable-days)



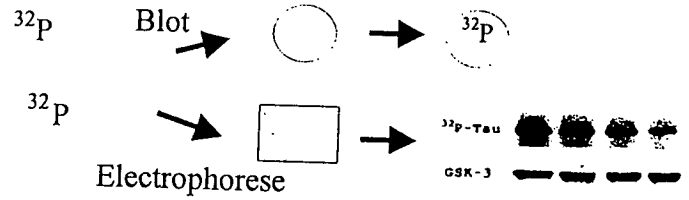
2. Immunoprecipitate the kinase (~4 hr)



3. Set-up and perform kinase reaction (hours)



4. Perform phosphocellulose assay or SDS-PAGE assay (hours-day)



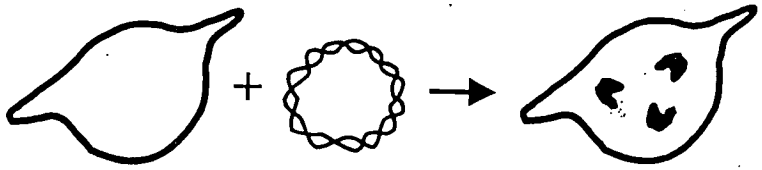
Assay Time ~Days

Fig. 4

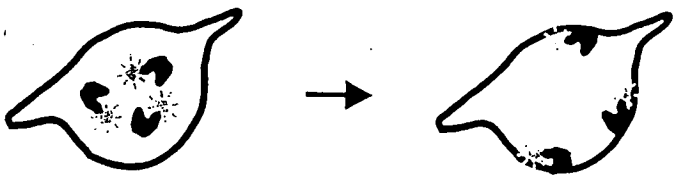
(prior art)

Measurement of Protein Location (via GFP Tag)

1. Develop stably transfected cell lines carrying the overexpressed GFP-tagged protein



2. Fluorescent imaging and pattern recognition

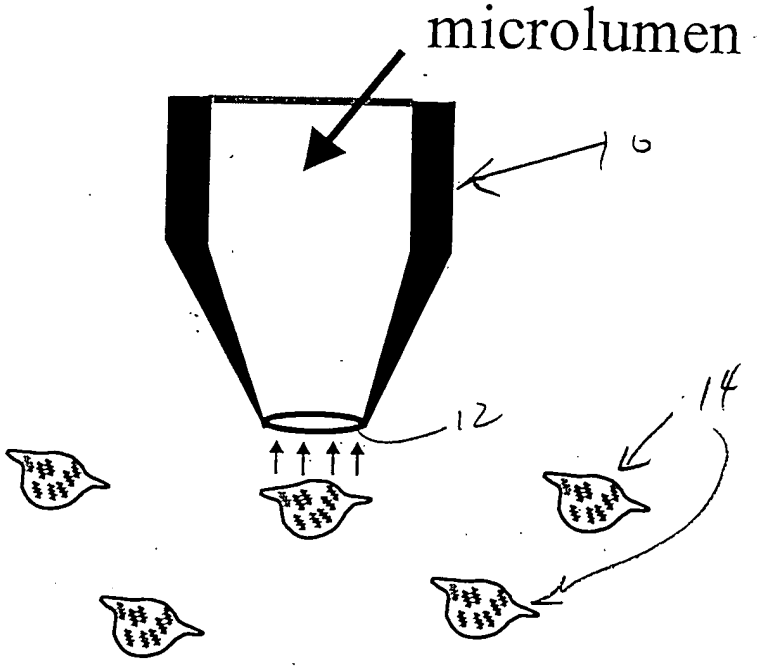


3. Infer protein activity from location

Assay Time ~Minutes

Fig. 5A

Single



Multiple

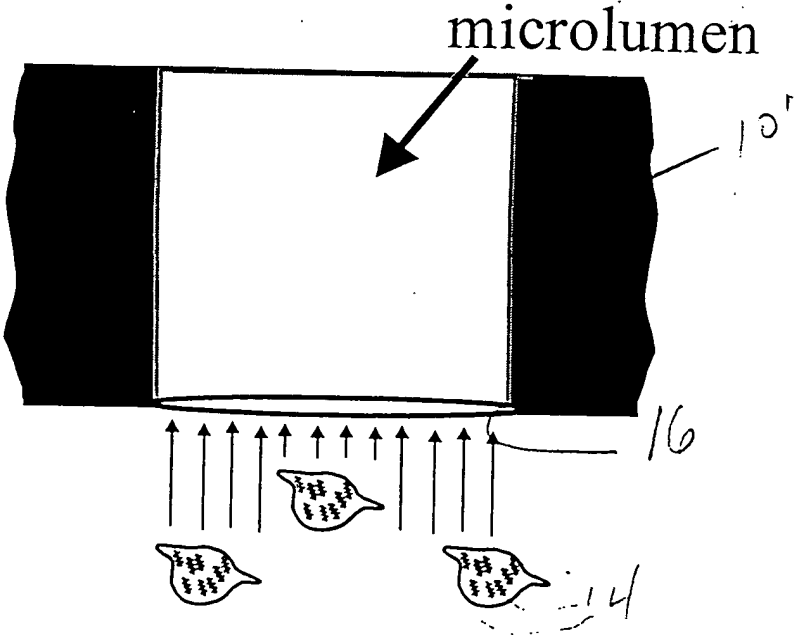
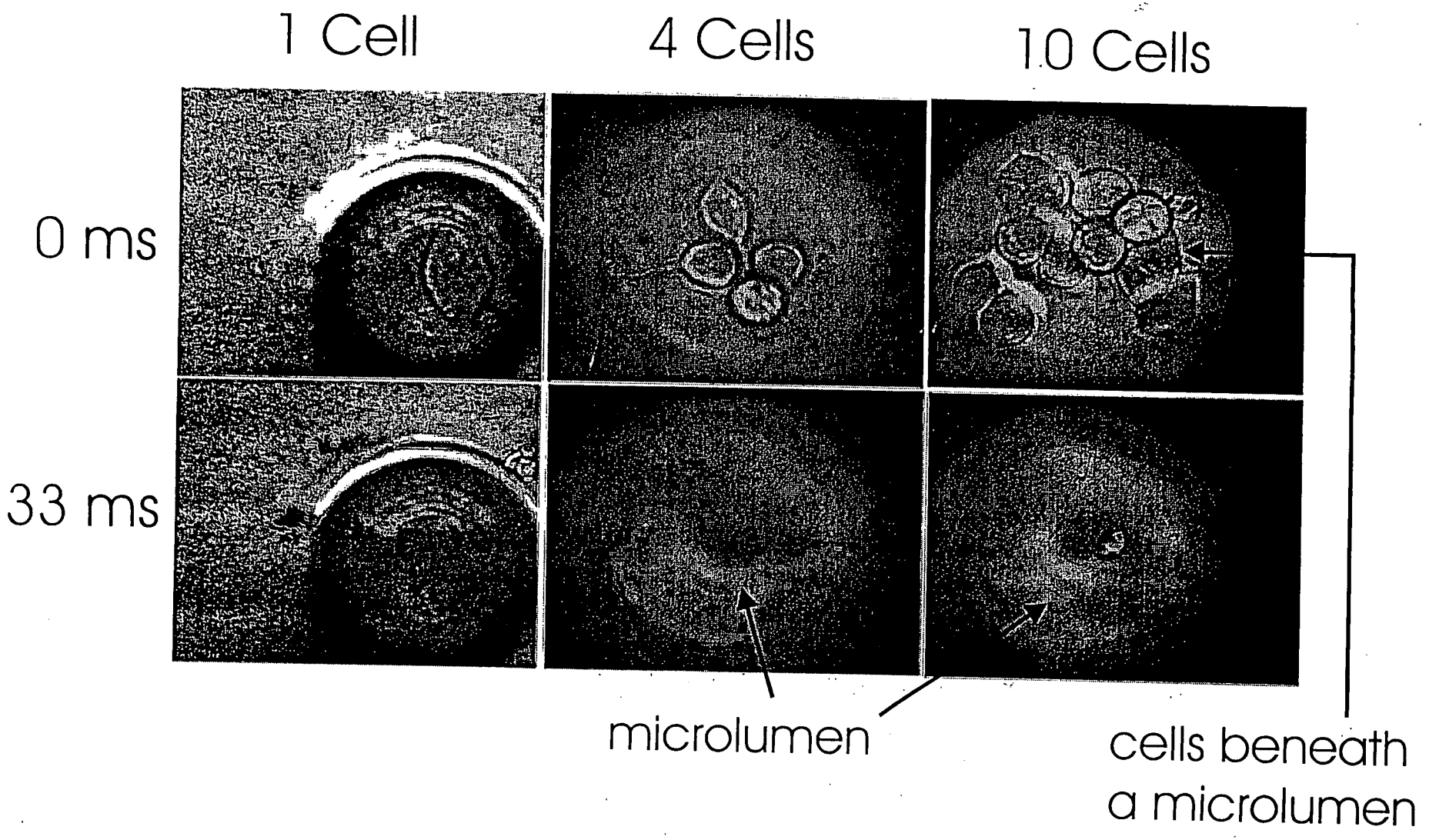


Fig. 5B

Performing "Population Average" Measurements



Single Cells or Population Averages

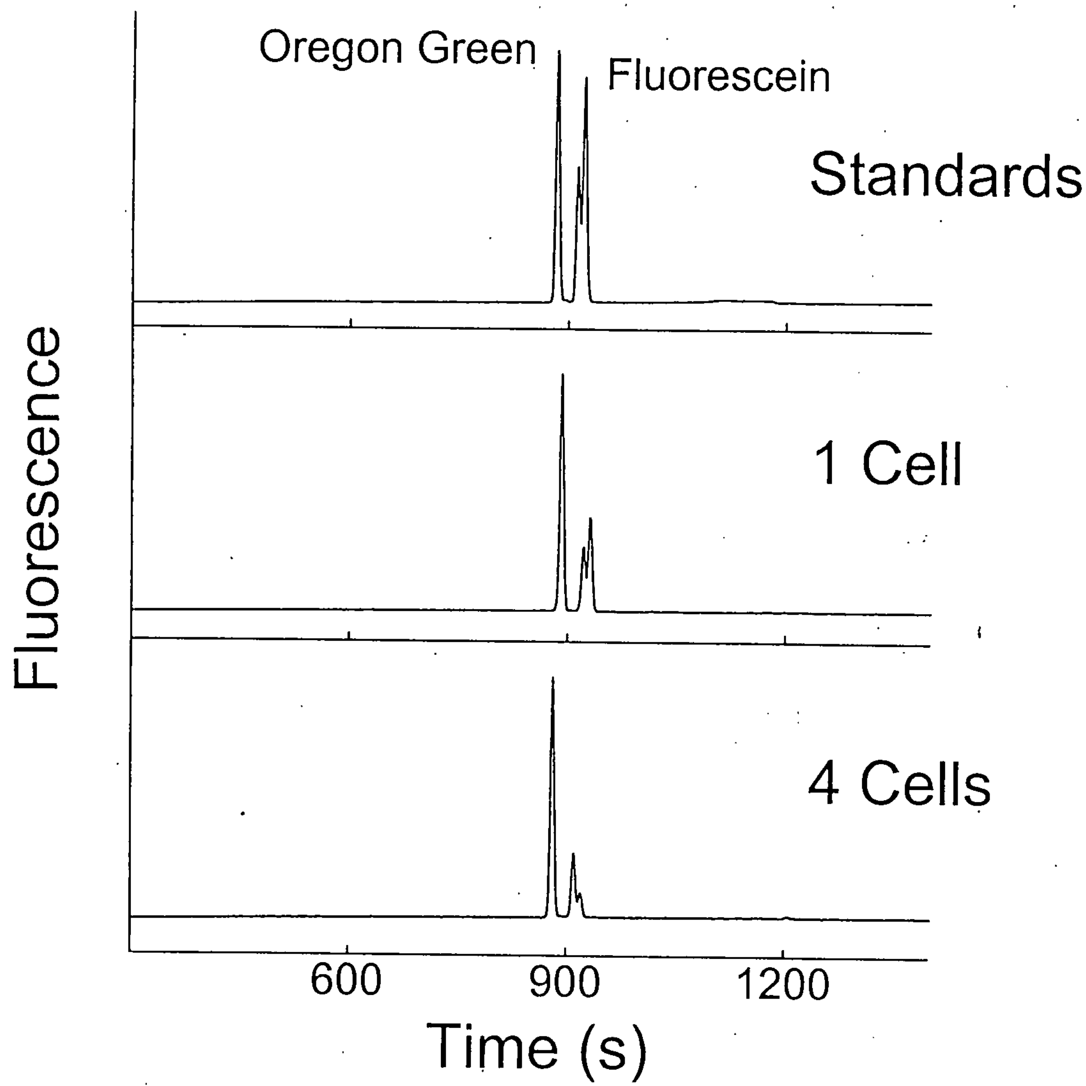


Fig. 5C

Fig. 6A Sampling a Portion of a Cell

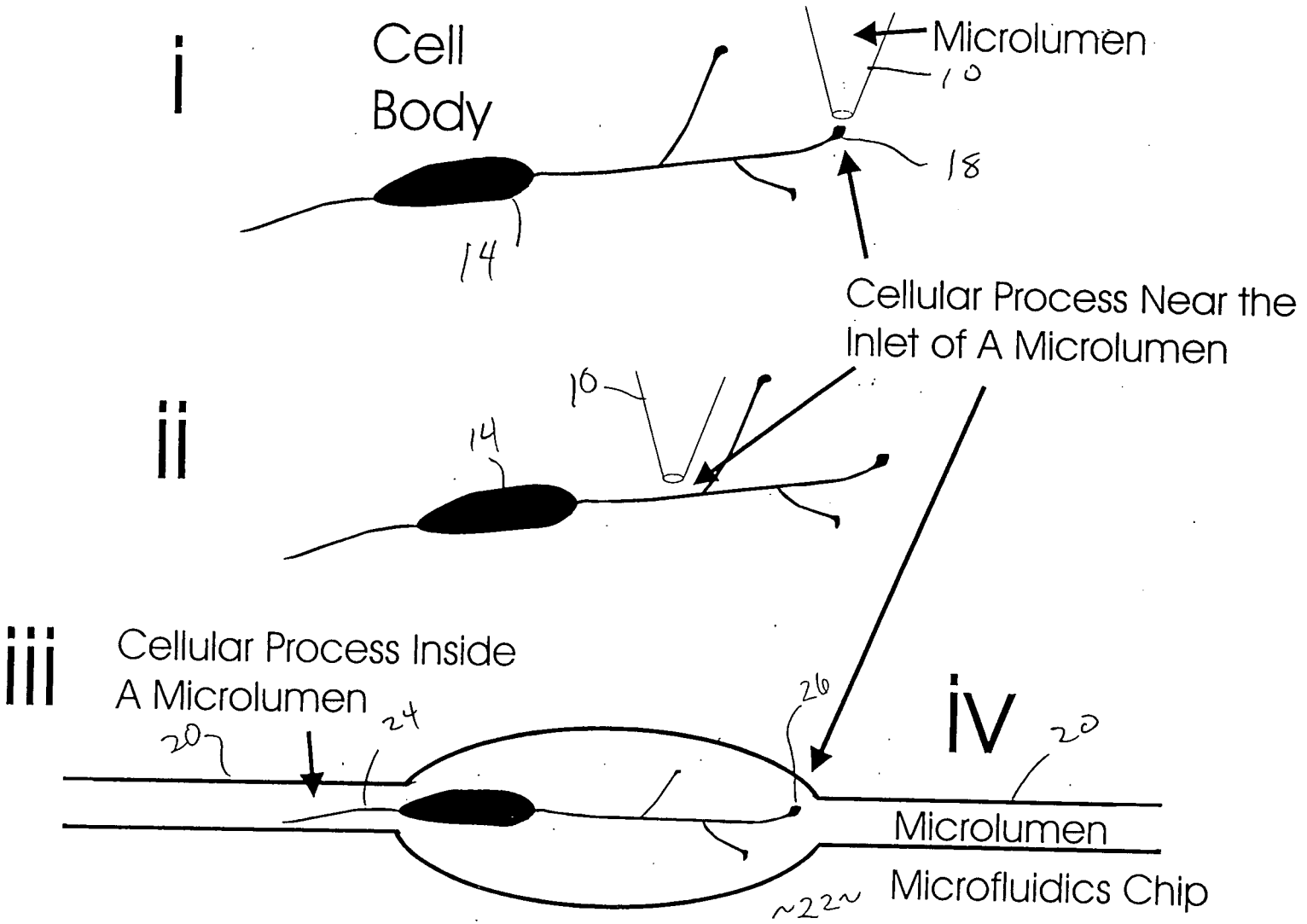


Fig. 6C

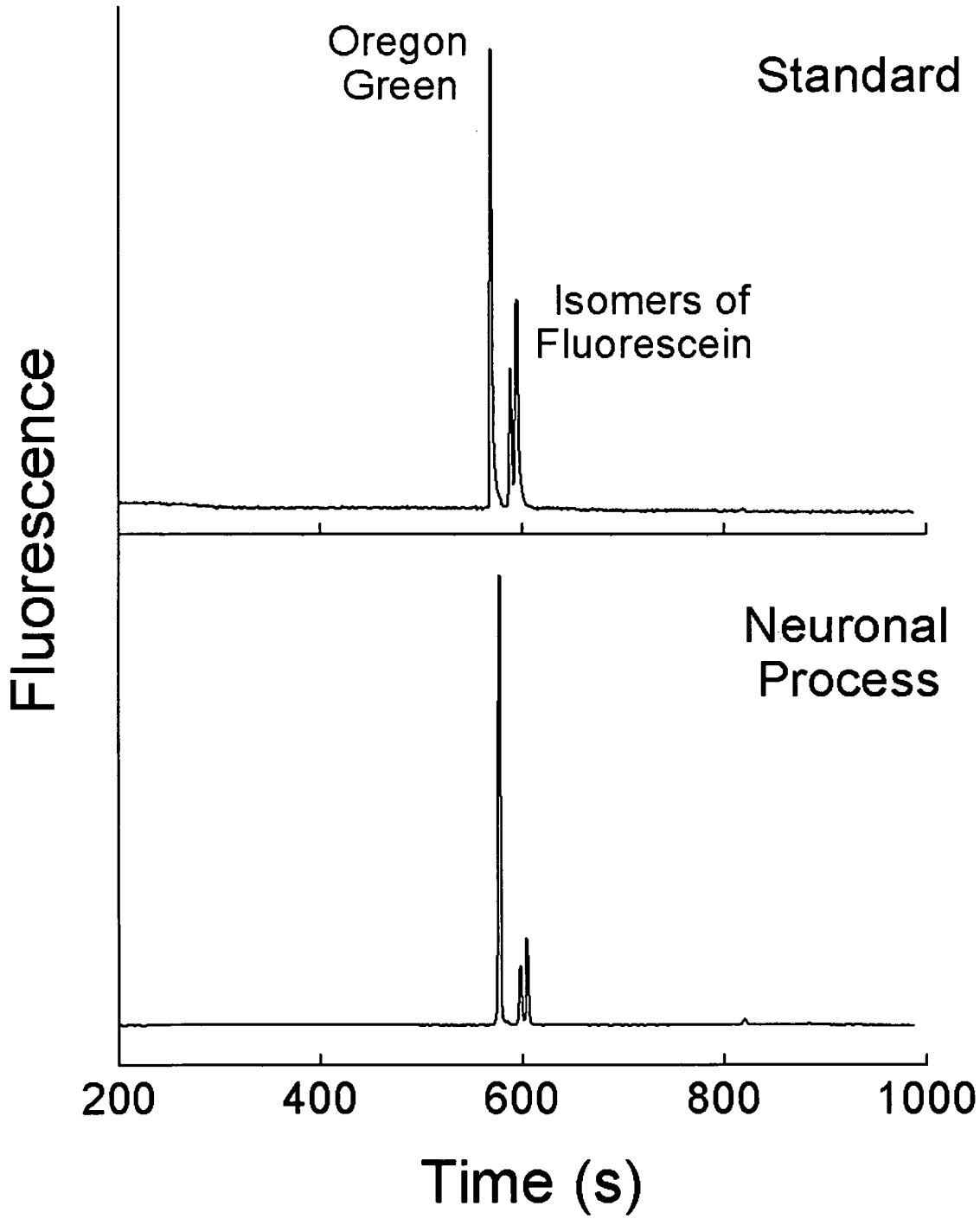

Analyzing A Neuronal Process
Oregon Green
Standard
Isomers of Fluorescein
Fluorescence
Neuronal Process
200
400
600
800
1000
Time (s)

Fig. 8

Loading Single Cells With Enzyme Substrates

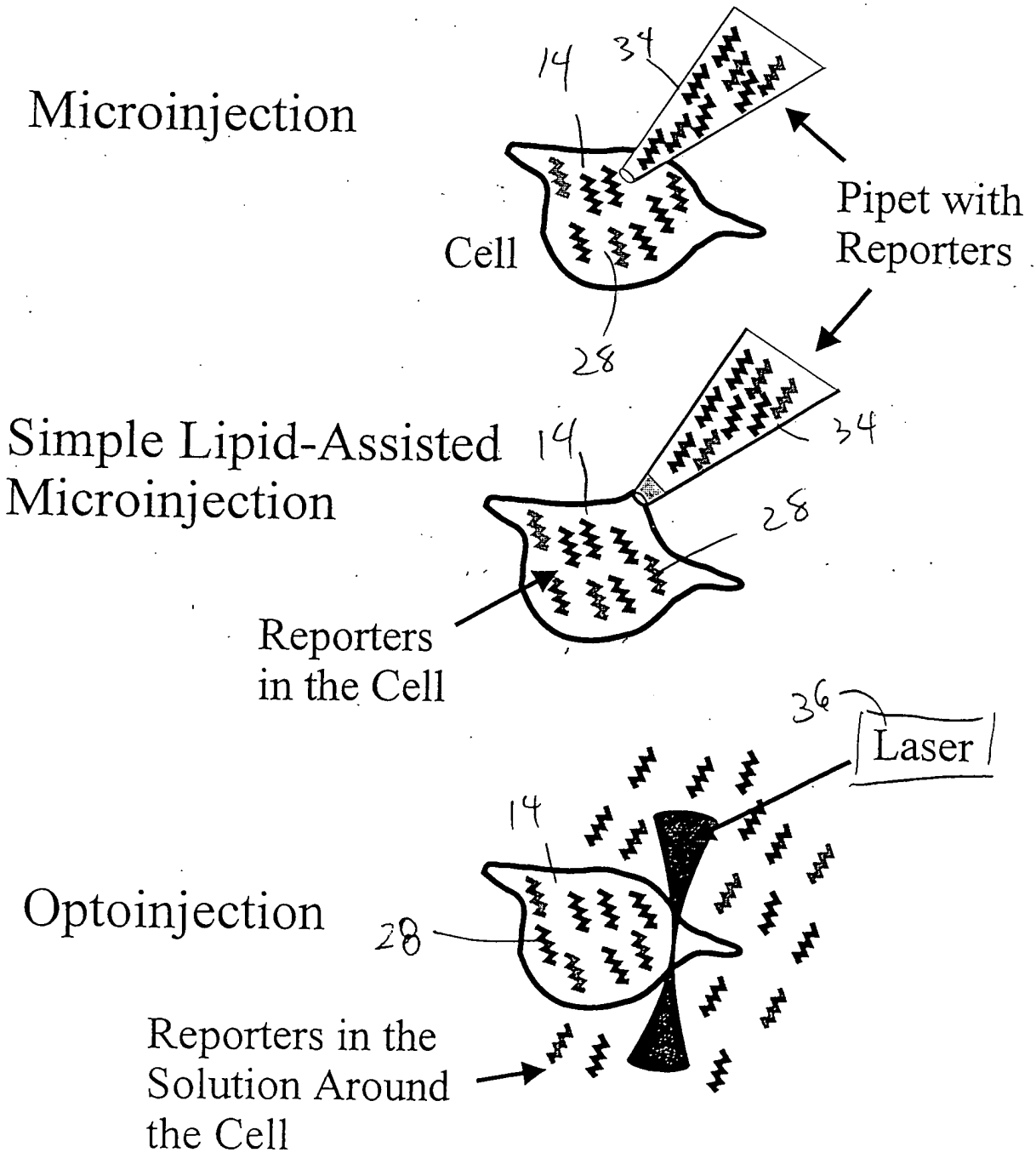
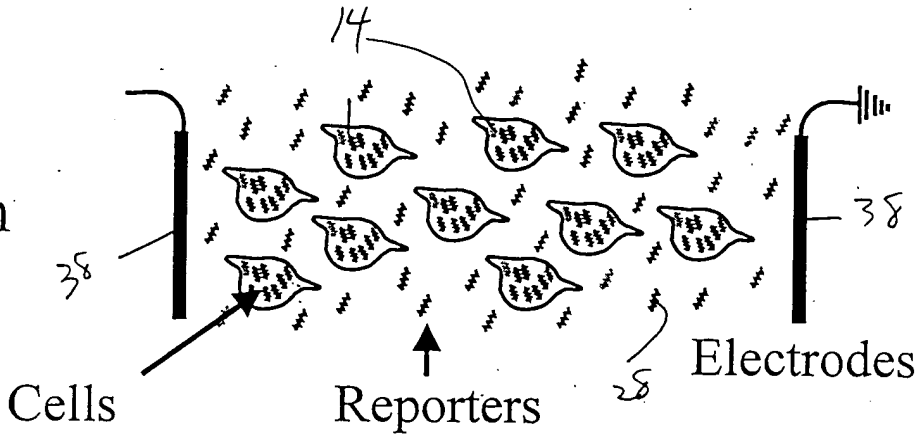


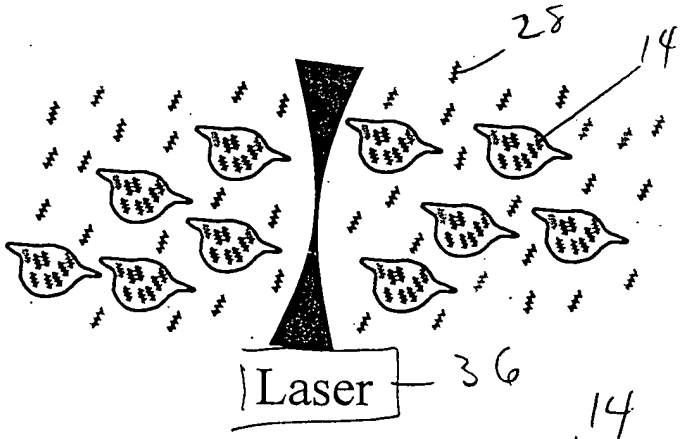
Fig. 9

Loading Multiple Cells With Enzyme Substrates

Electroporation



Optoporation



Passive Techniques

- Pinocytosis
- Vesicle Fusion
- Membrane-Permeant Substrates

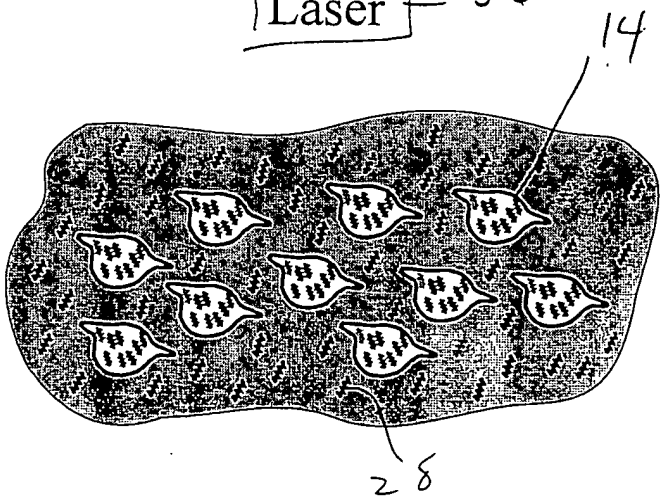


Fig. 10

Nuclear-Localized Substrate for PKC

Fluorescence Image Transmitted Light Image

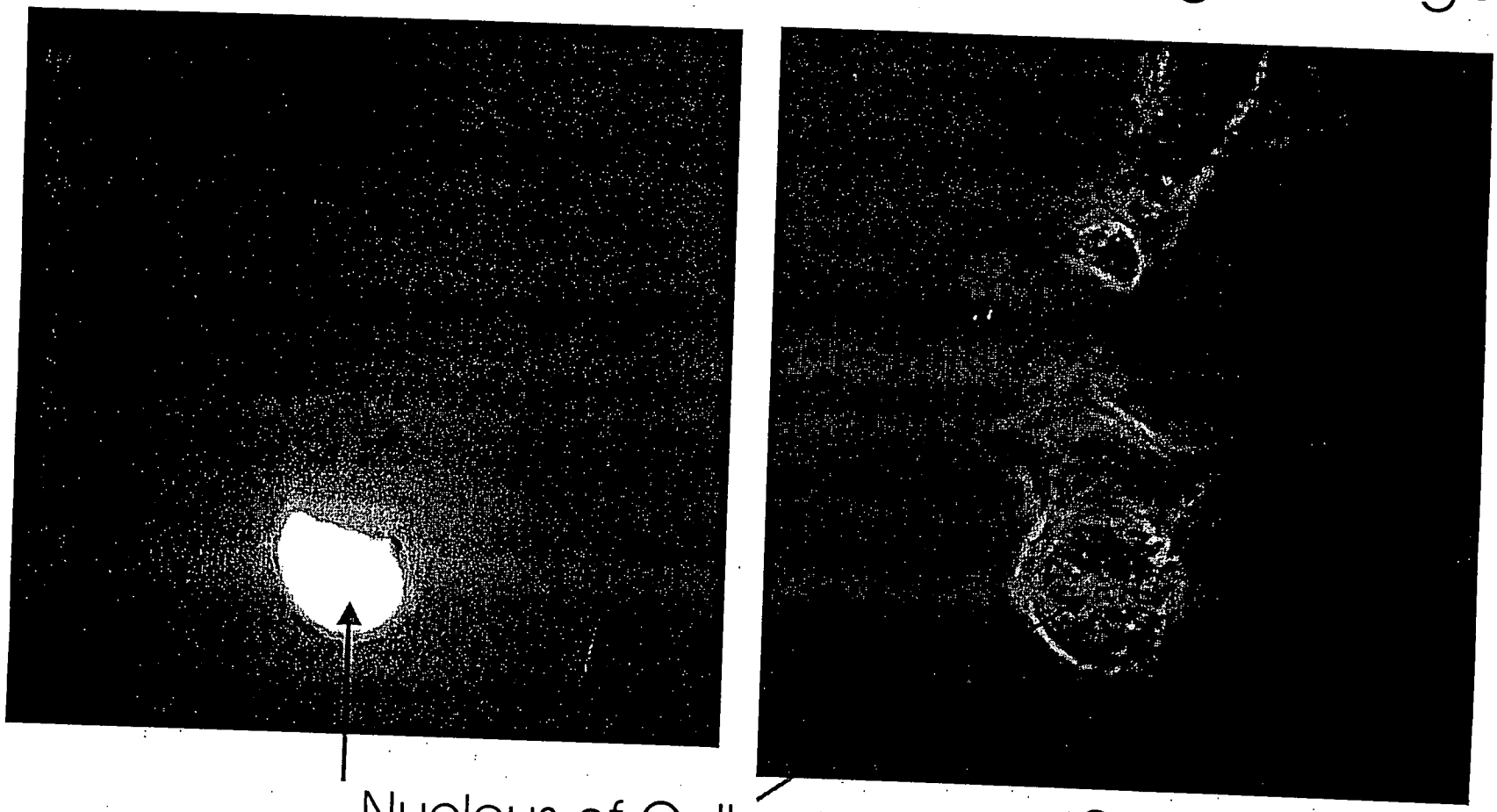


Fig. 11

Coupling to Other Technologies

Proteomics

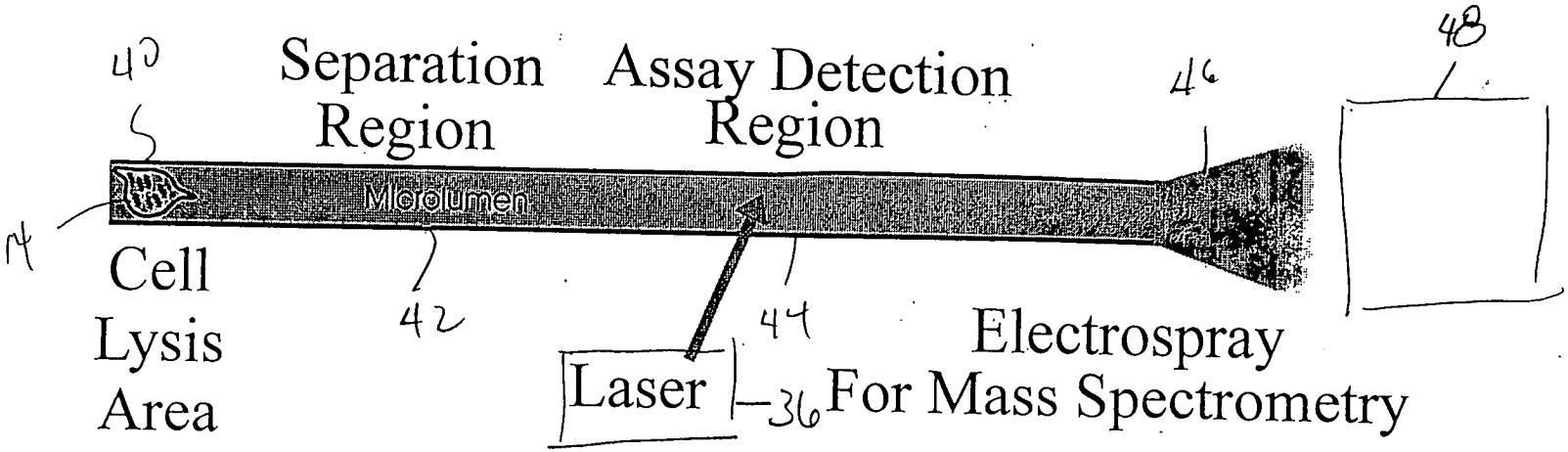


Fig. 12A

Coupling to Other Technologies

Genomics

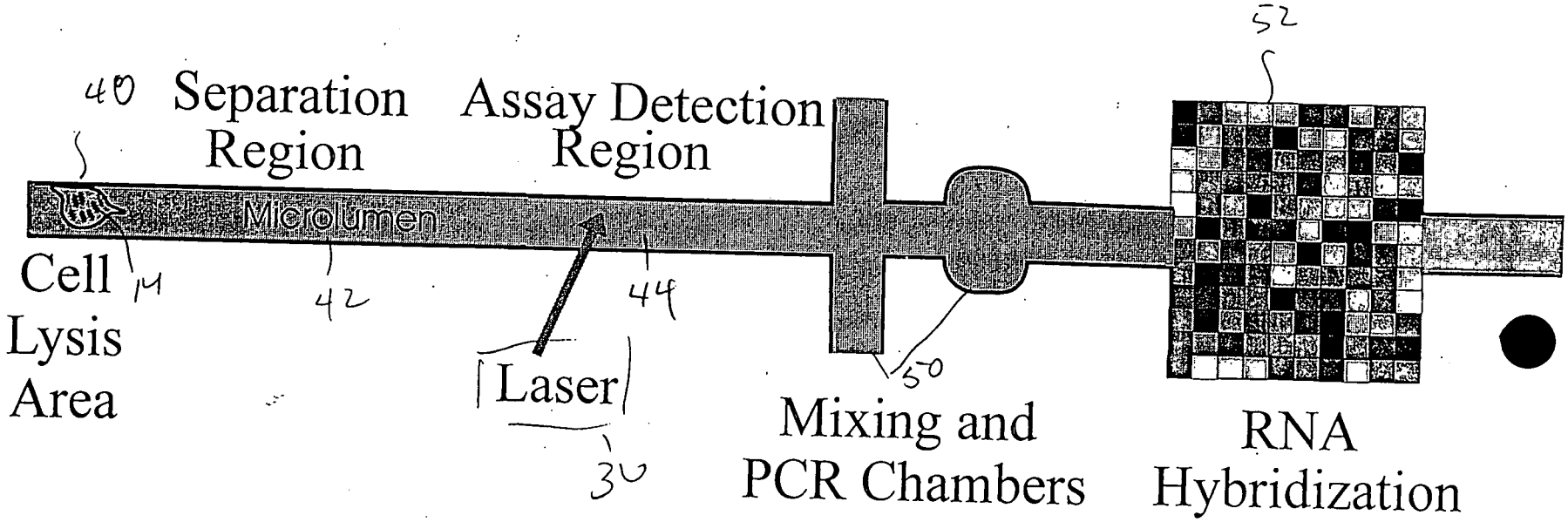


Fig. 12B

SIGNAL TRANSDUCTION MICROCHIP

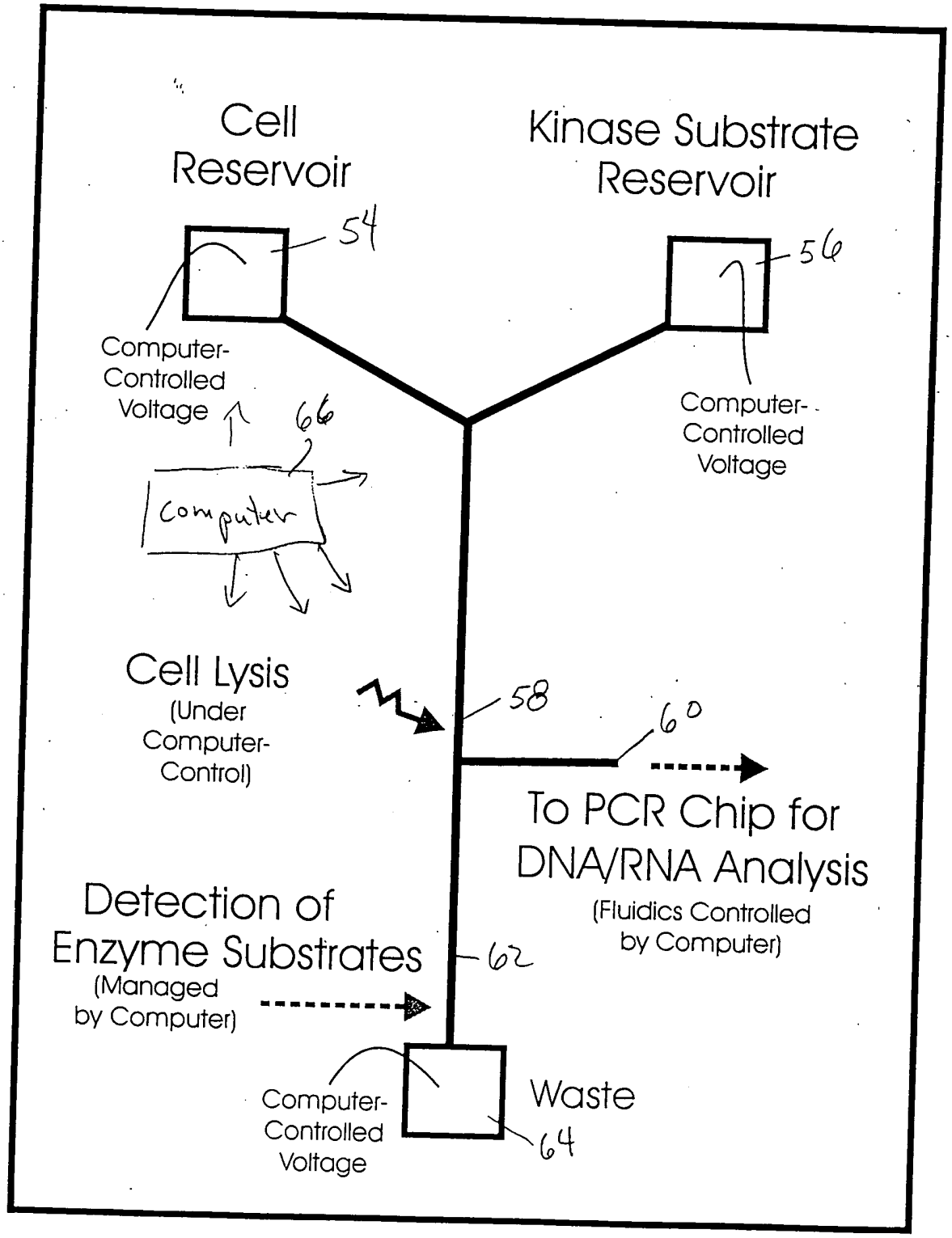


Fig. 13

Coupling to Other Technologies

Flow Cytometry

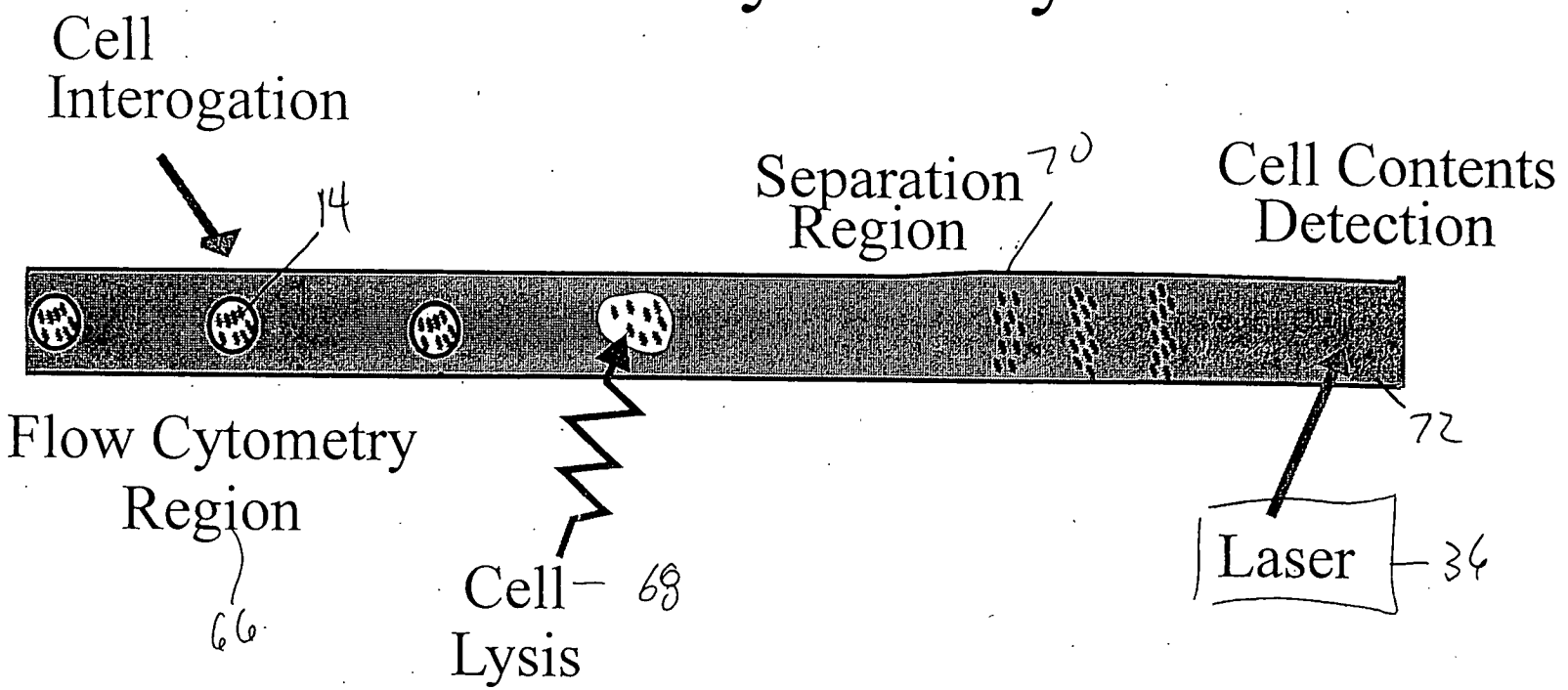
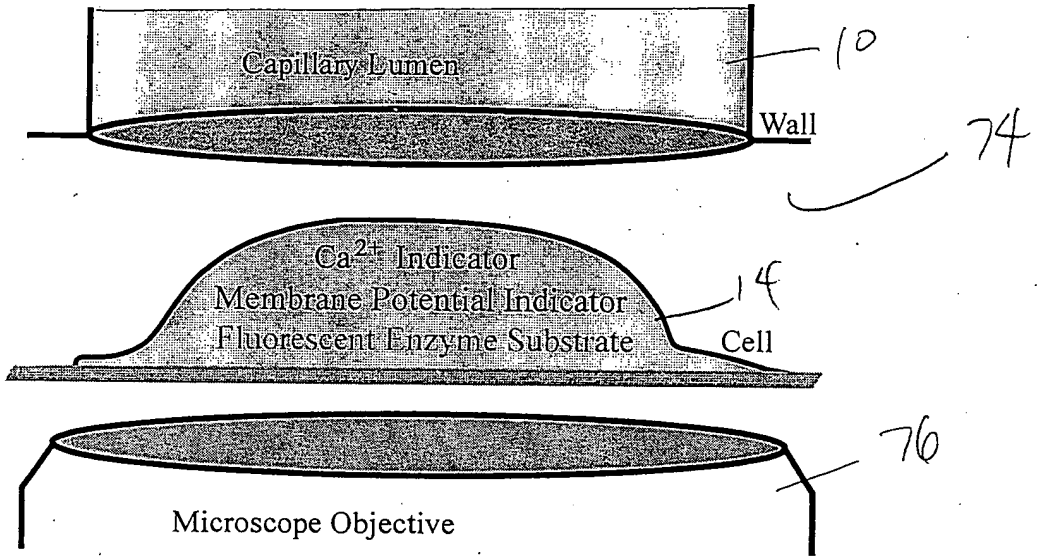


Fig. 14

Integration With Other Cellular Analysis Methods

Fluorescence Imaging



Patch Clamp

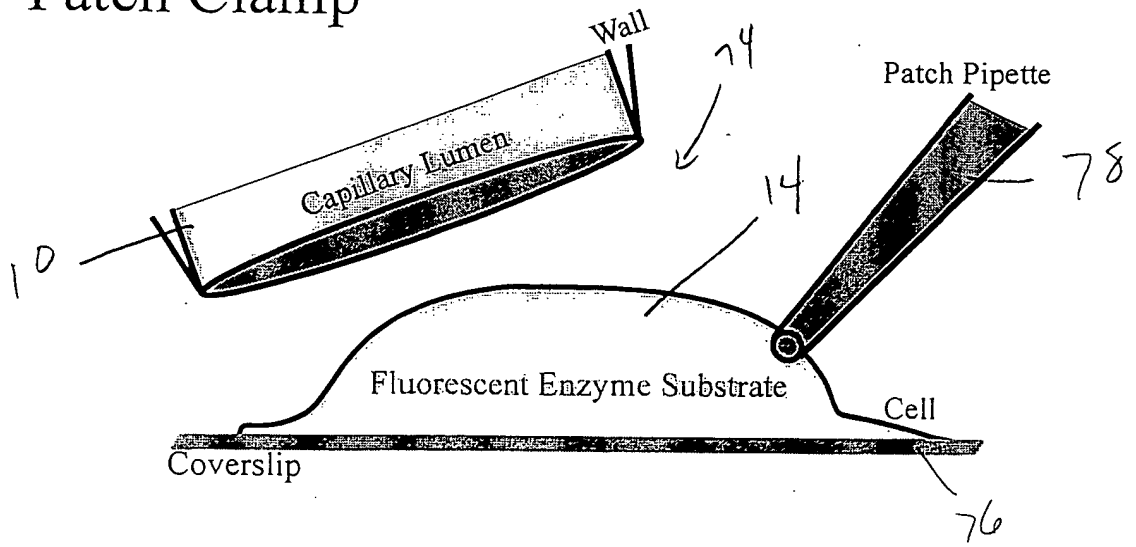


Fig. 15A

Profiling Signal Transduction Pathways in Cells with Four Reporters

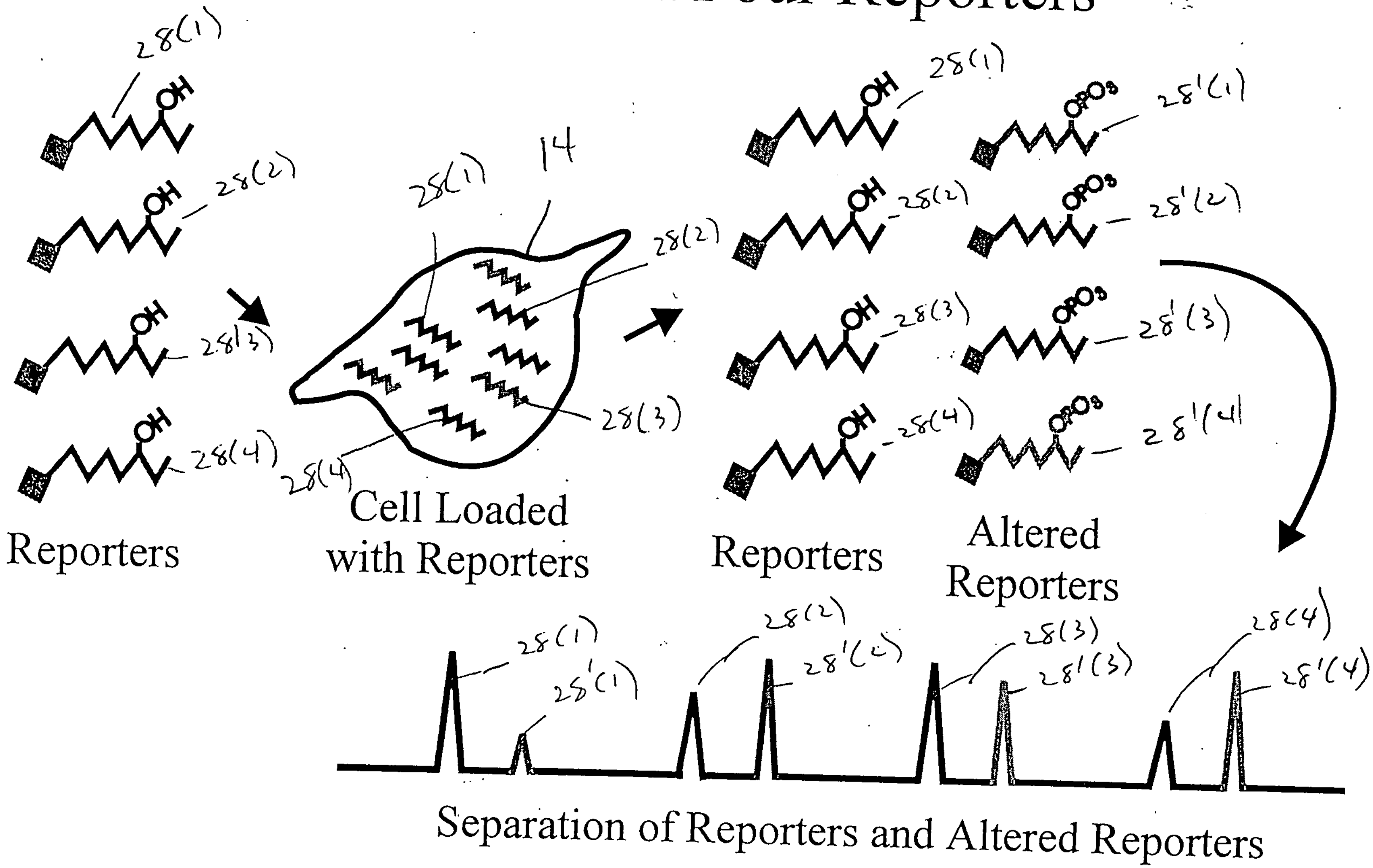


Fig. 17

Profiling Signal Transduction Pathways
in Cells with Ten Reporters

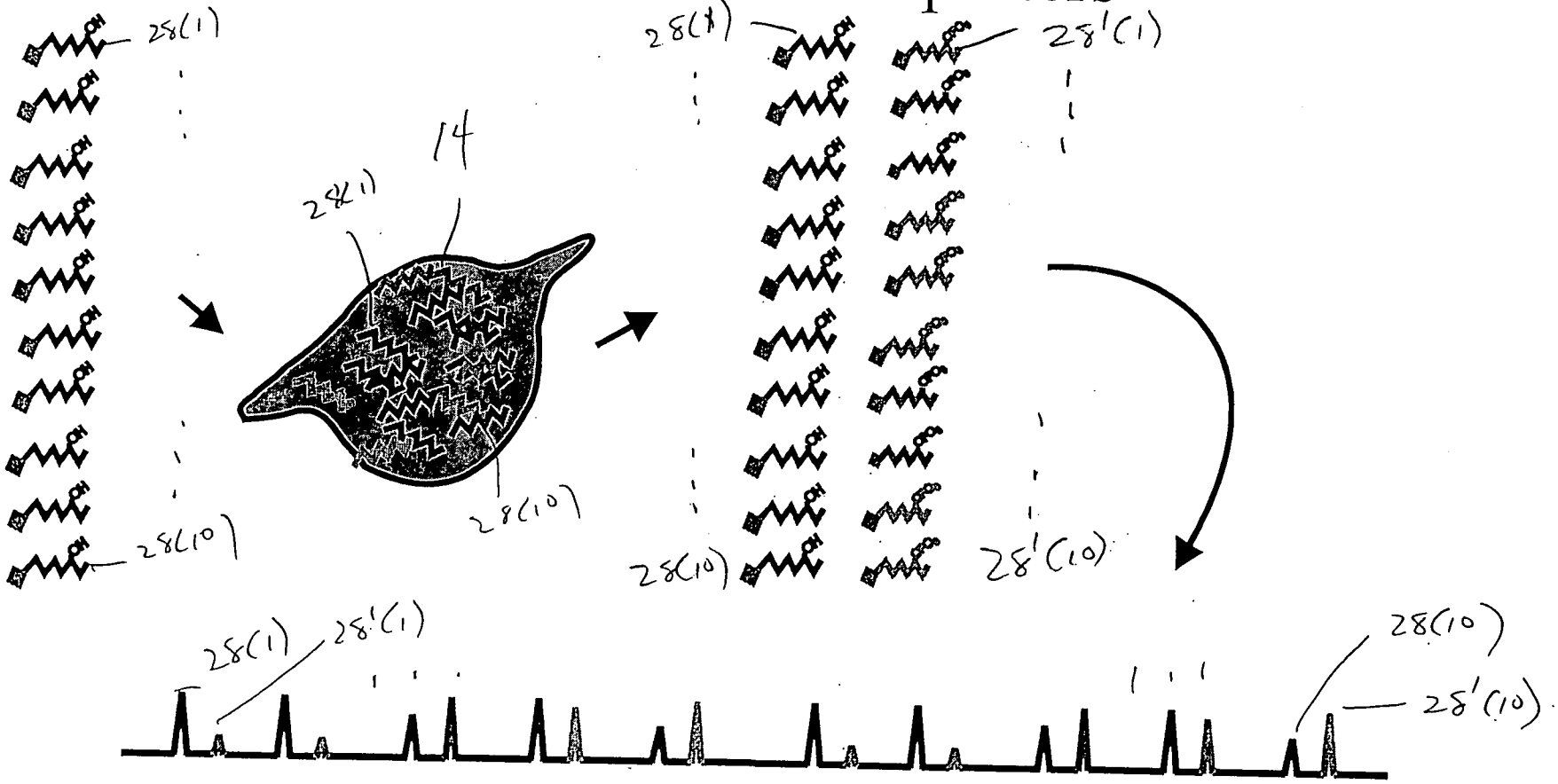


Fig. 19

Applications

- Drug Discovery and Validation

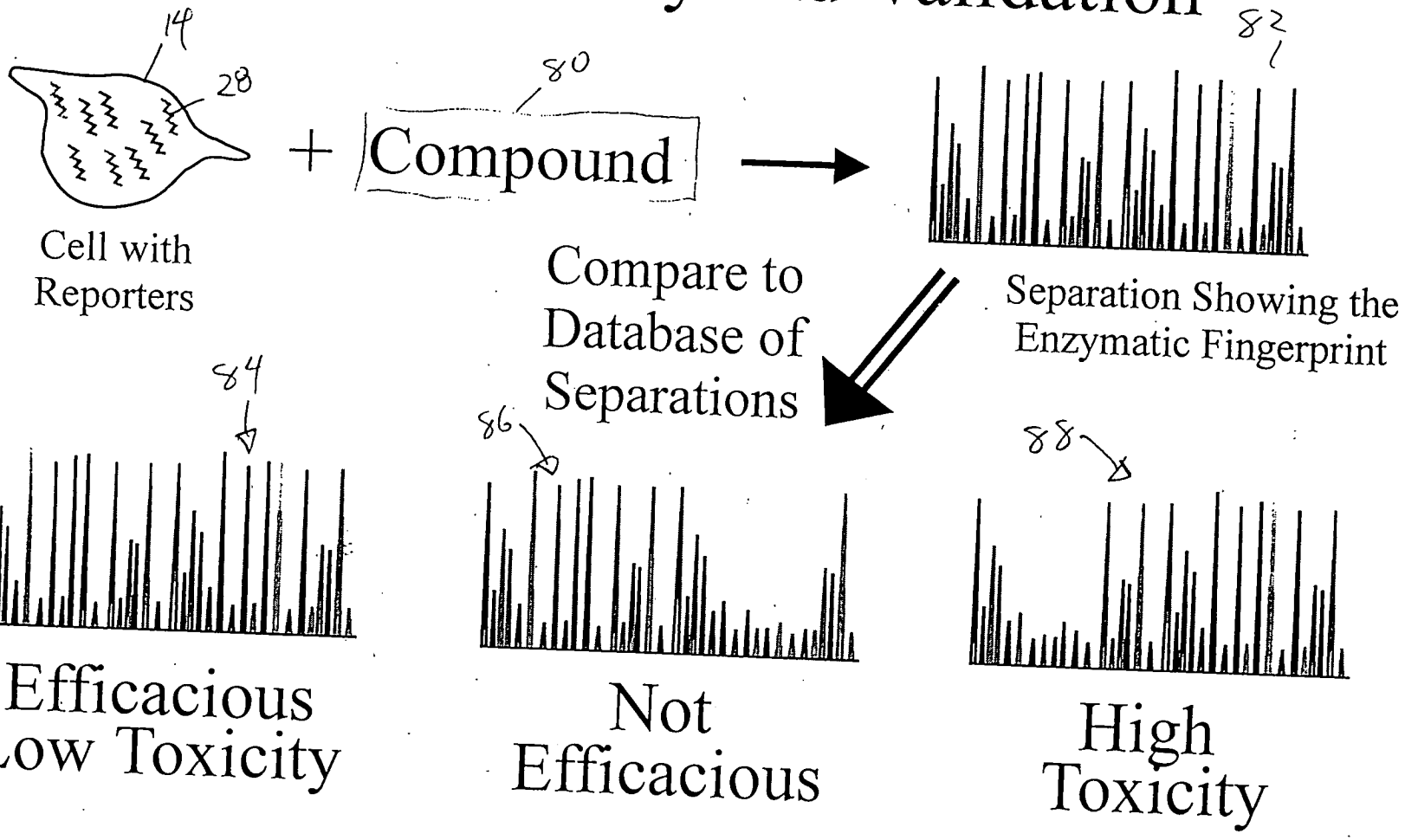


Fig. 20

Identifying the Cellular Targets of Compounds

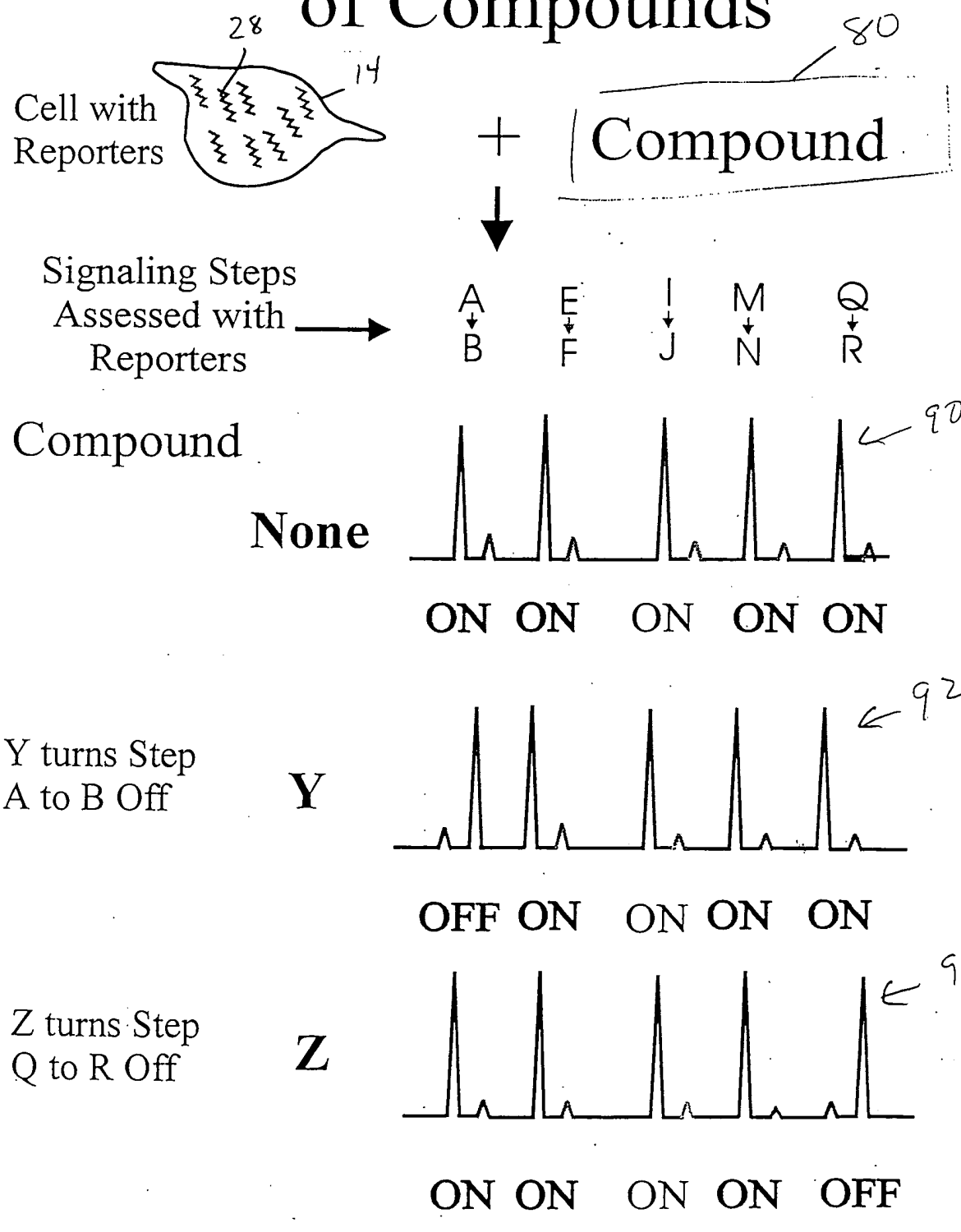


Fig. 21

Applications

- Diagnostics and Prognostics

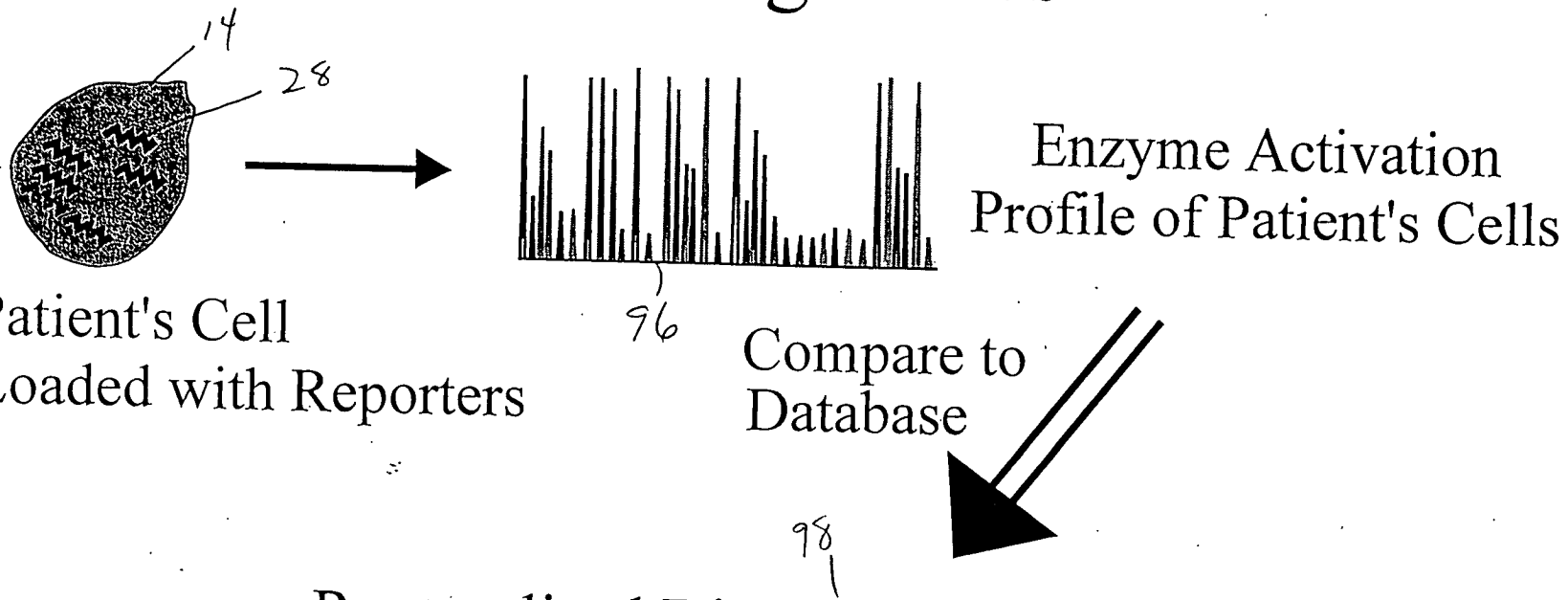
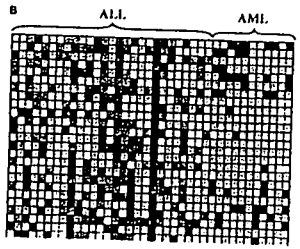
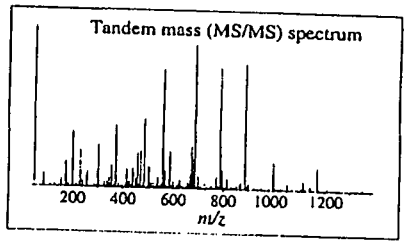
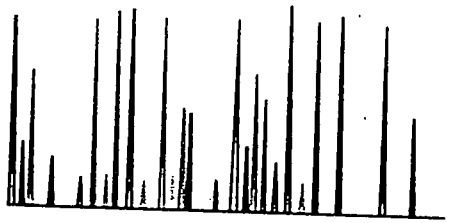


Fig. 23

Analysis of Biologic Systems







DNA Arrays

Mass Spec., Protein Arrays

Protein Activity Maps

Genomics

Proteomics

Signaling

Fig. 24

Serial Analysis of Cells

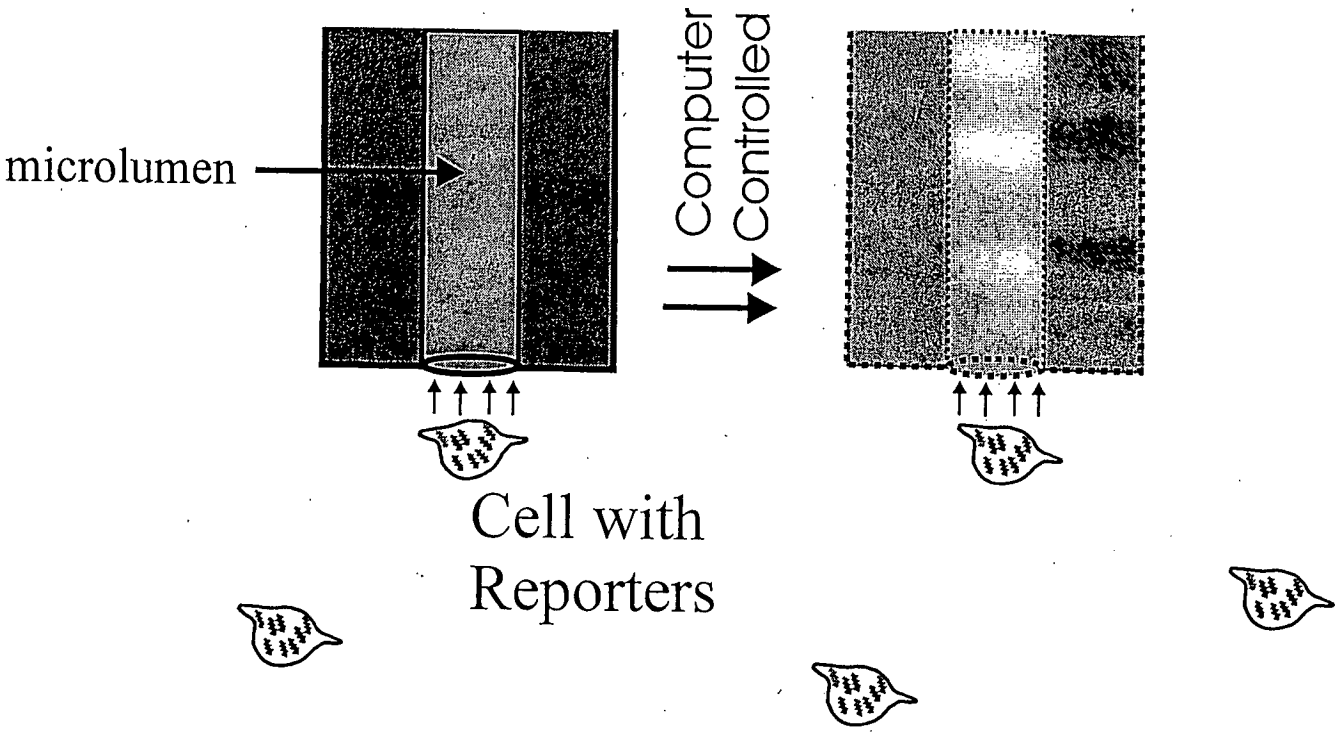
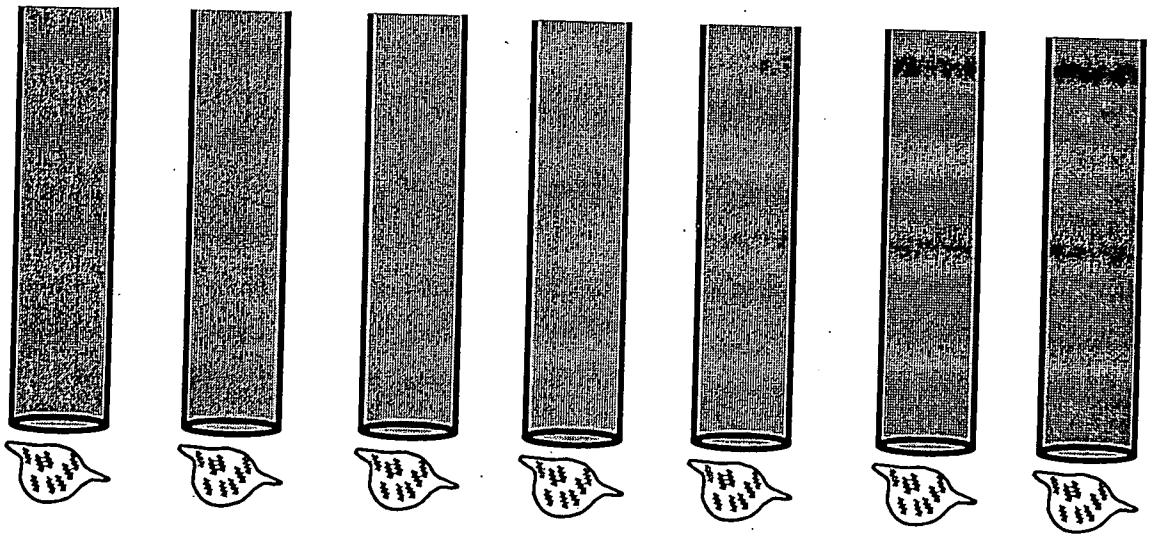


Fig. 25

Parallel Processing of Cells-

Arrays of Separation Channels



Computer-control of microlumen alignment over cells, lysis, and/or other steps.

Fig. 6B

Sampling the Contents of a Neuronal Process

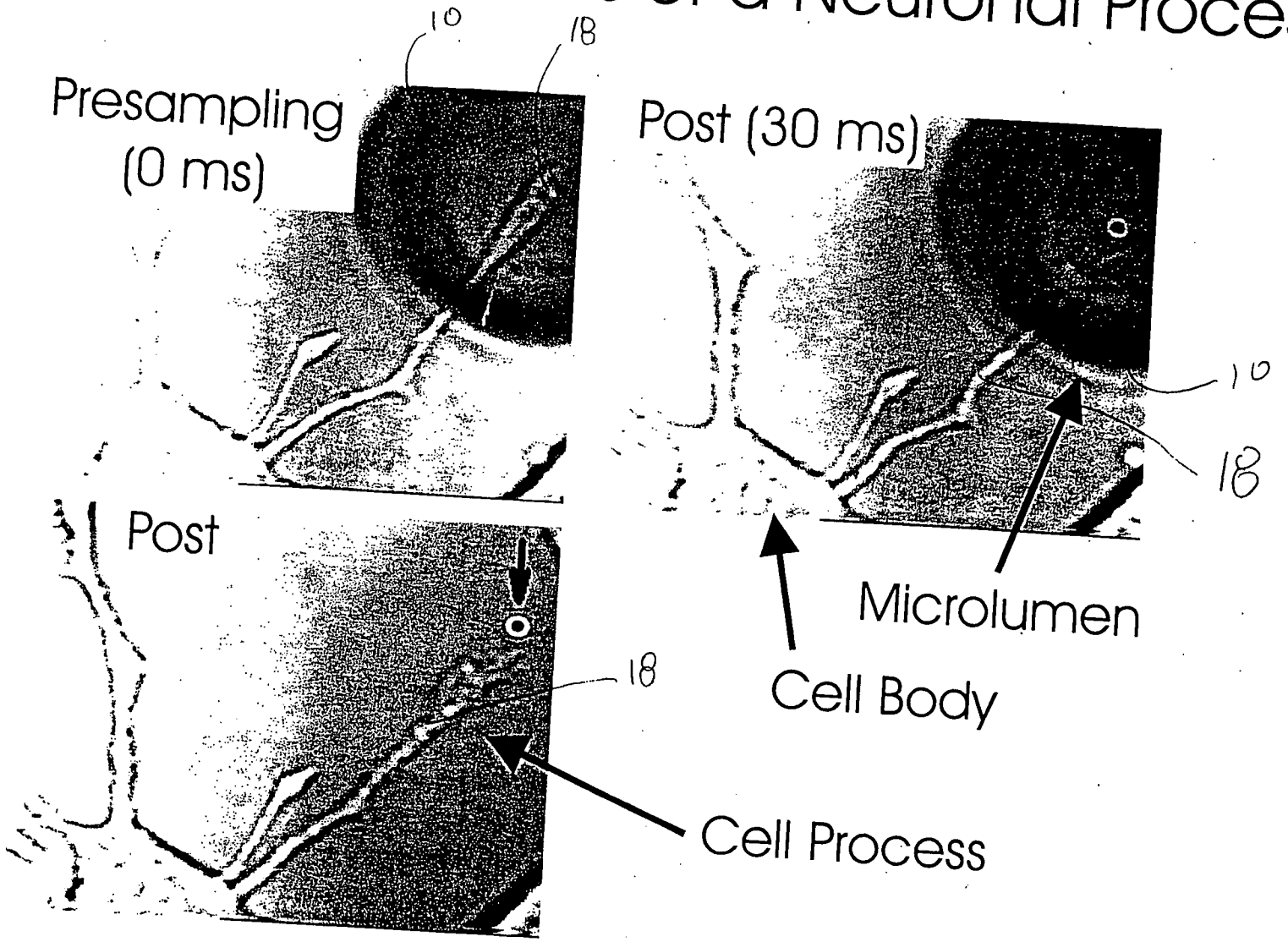


Fig.7a Cell Assay

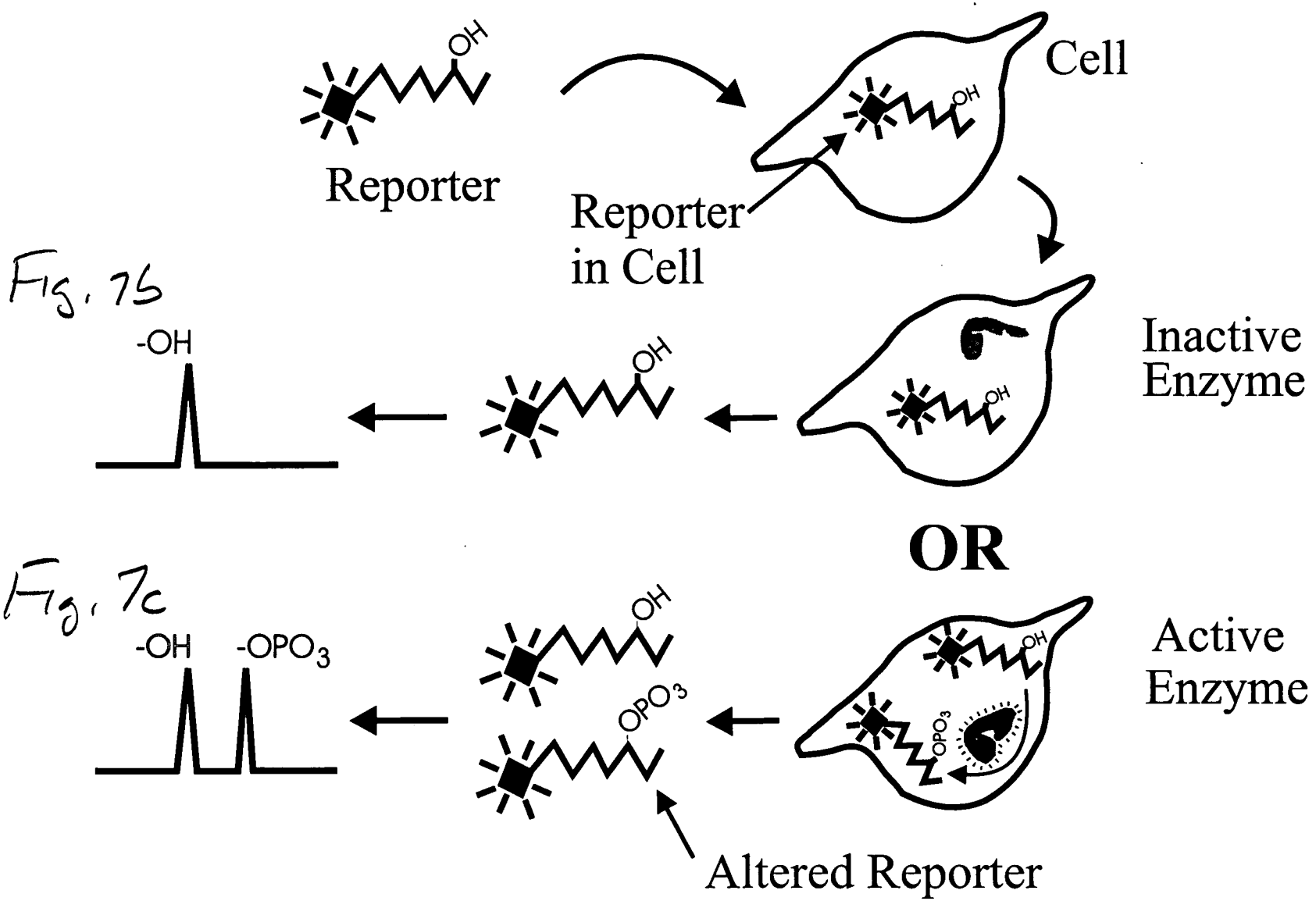


Fig. 15B

Profiling Signal Transduction Pathways in Cells with Three Reporters

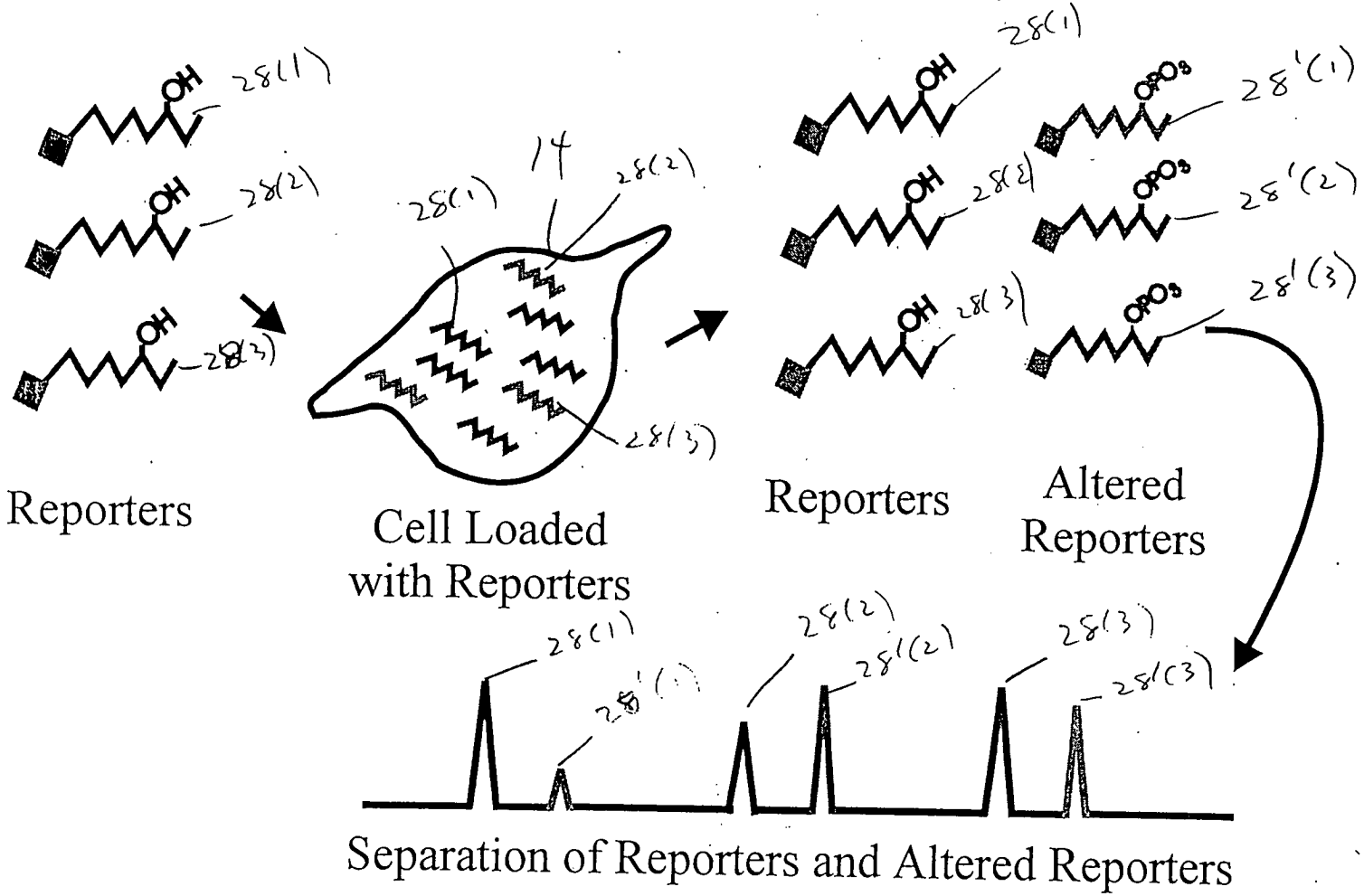


Fig. 16

Profiling Signal Transduction Pathways in Cells with Five Reporters

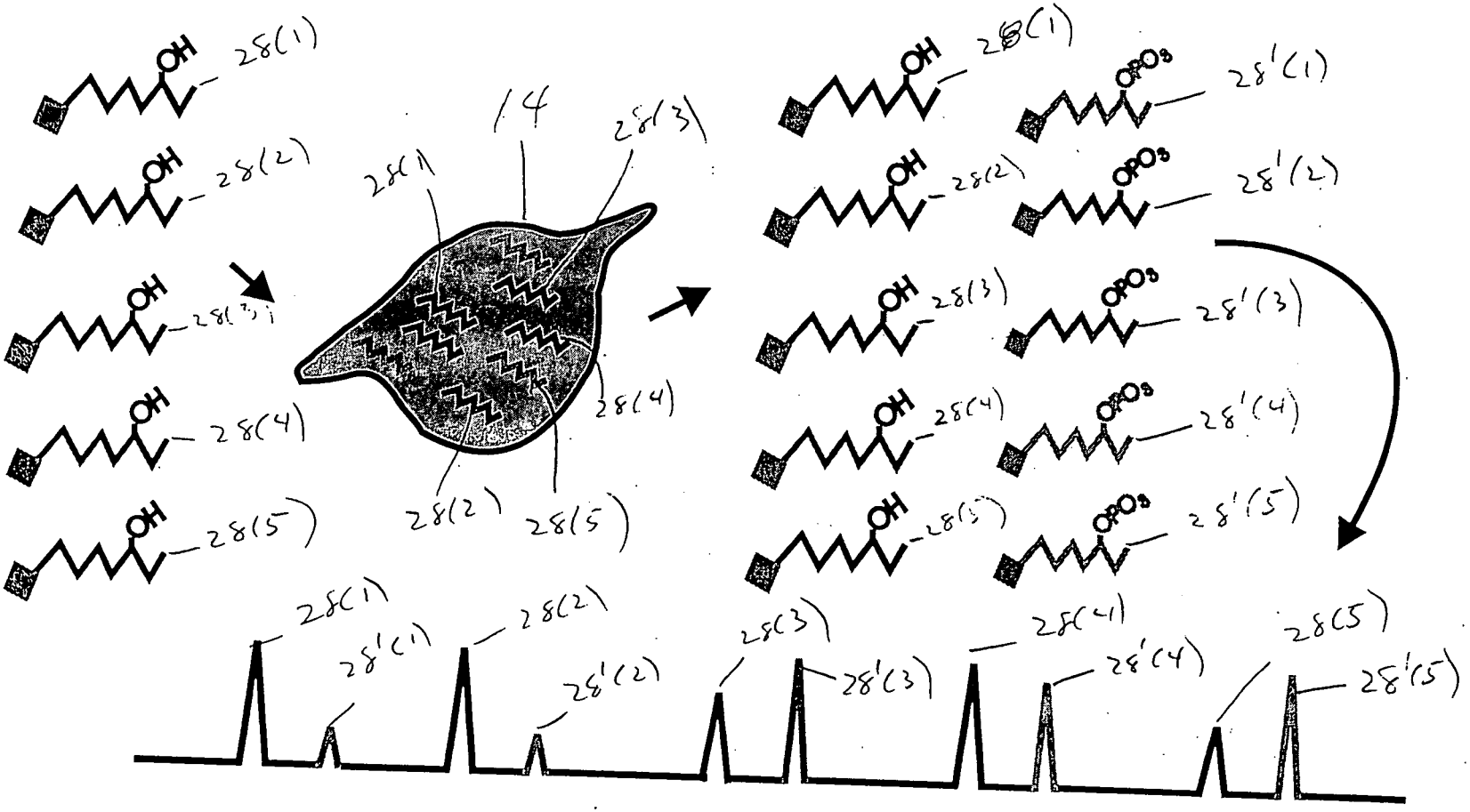


Fig. 18

Profiling Signal Transduction Pathways in Cells with Many Reporters

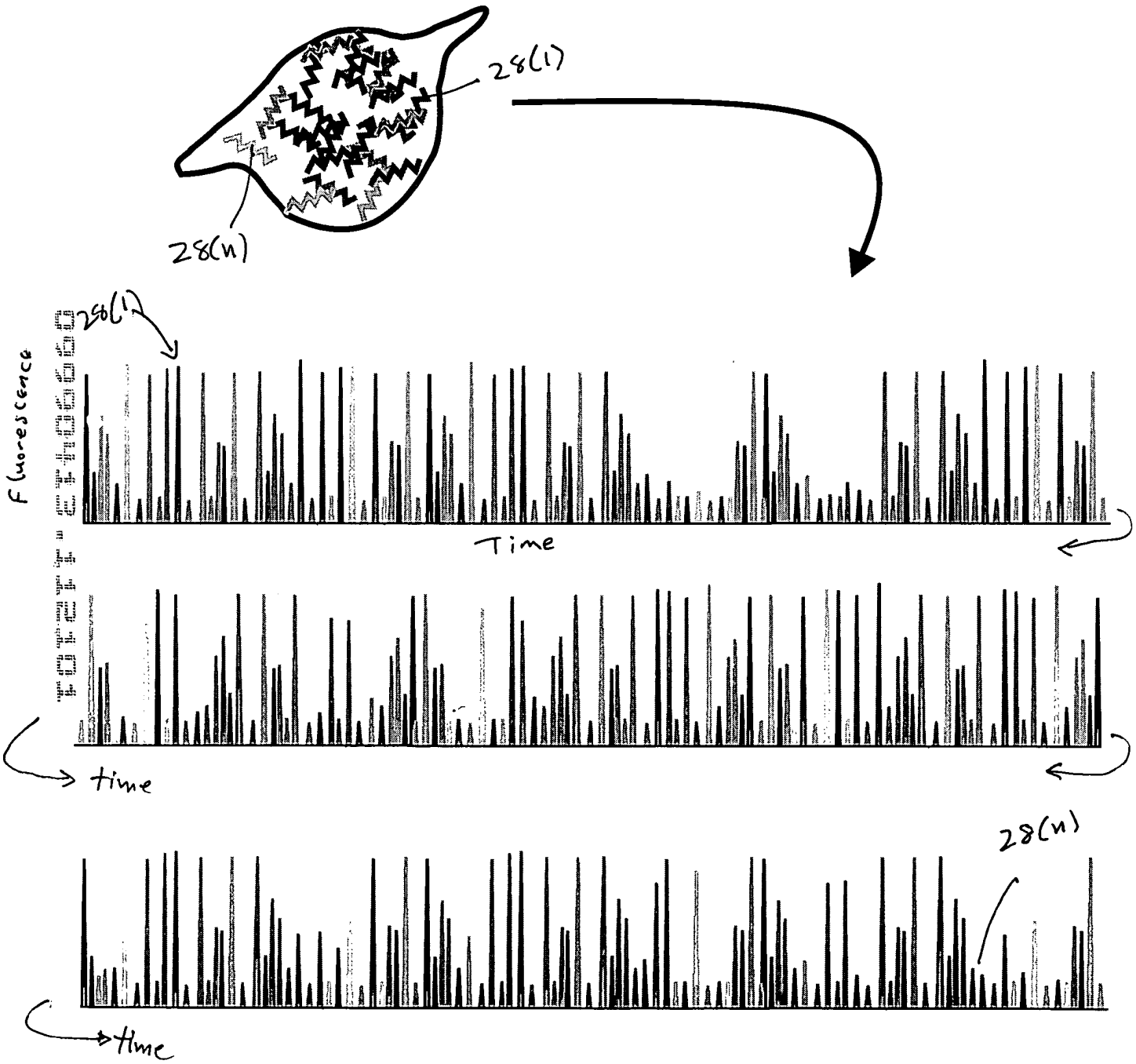


Fig. 22

Identifying and Targeting Pre-Disease or Disease States

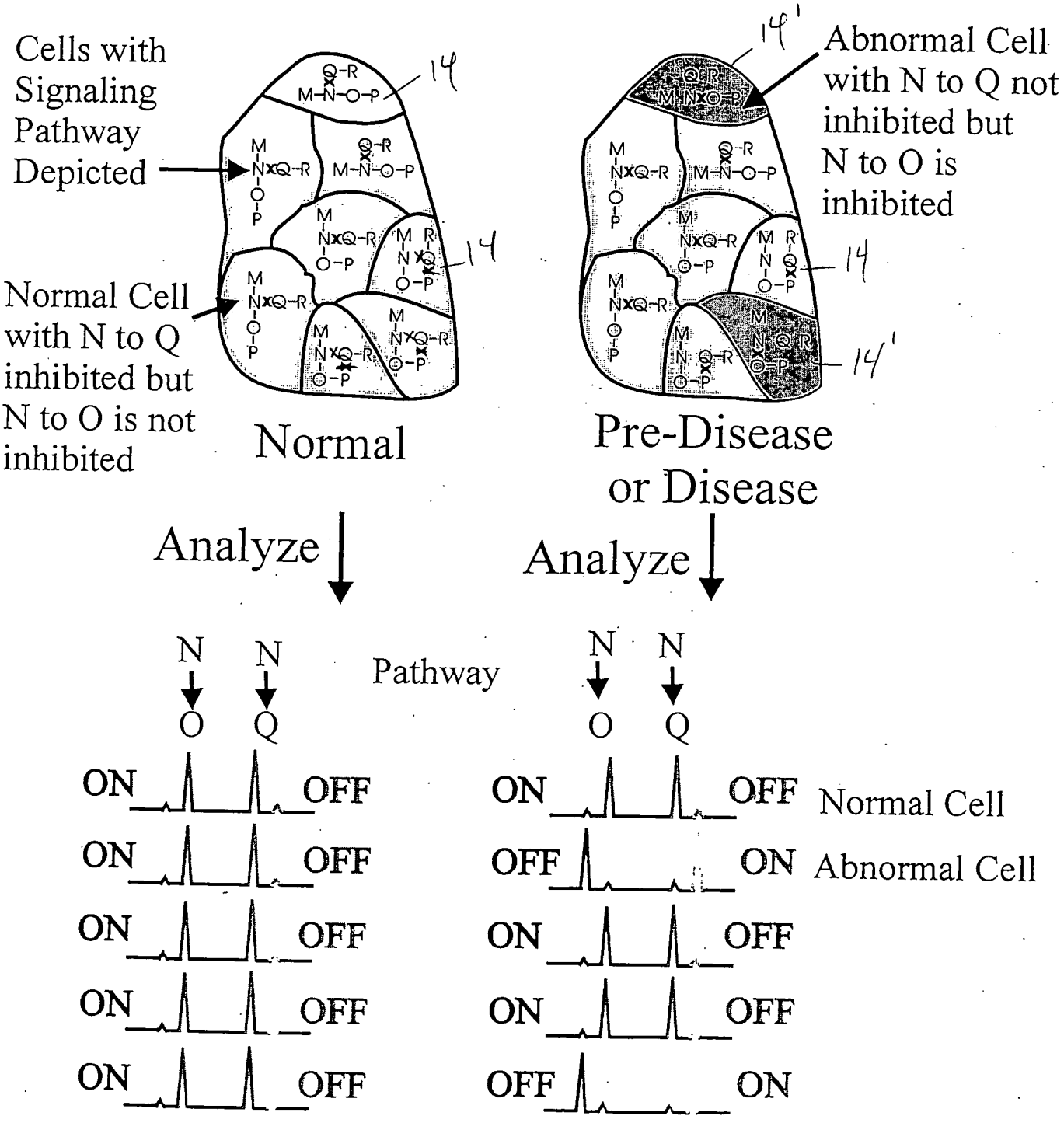


Table I
Influence of the Intracellular Environment

Cellular Property	Is it the same after removal from the cell?
1. DNA, RNA (sequence, quantity)	Yes
2. Protein (identity, conc.)	Likely
3. Activity	Usually Not

Table II

Cellular Properties Are Distinguished By Their Timescales

DNA & RNA "Genomics"	Minutes - Years
Protein "Proteomics"	Seconds - Hours
Activity "Signaling"	Milliseconds - Seconds

Table III

A Sampling Of Available Technologies

Field	Property	Technologies
1. Genomics	DNA, RNA	DNA Arrays
2. Proteomics	Protein Identity & Conc.	Protein Gels/Arrays Mass Spec.
3. Signaling	Activity	GFP-Based Methods Critical Need